REMARKS

I. Status of claims

Claim 1, 6, and 36 are amended.

Claim 2 is cancelled.

Claims 3-5, 7-35 and 37 are withdrawn.

Claims 1, 6, and 36 are pending.

II. Claim Amendments

In the Advisory Action mailed May 21, 2007 the examiner stated that the amendments filed April 30, 2007 raised "new issues." Applicant proposed the amendment from an agent that "interacts with Gadd45β" to an agent that "blocks suppression of JNK activation by Gadd45-beta" because the examiner refused to accept applicants' evidence that "interacts" was supported in the specification. It should first be noted that "agent" was in the original application as filed. The term "blocks suppression of JNK activation by Gadd45β" was in the claims as originally filed so not sure how this can be "new matter".

Additional support for "agents blocking suppression" is as follows:

Par	Comment
[00021] [00023]	Cell-permeable peptides, antisense, or small molecules are identified to perform this function.
[00051]	FIG. 40: antisense to Gadd45β results in JNK activation.
[00066] [00072]	Gadd45β suppresses JNK activation, and thereby apoptosis
[00076]	Gadd45β (114-160) was unable to associate with JNKK2
[00077]	Gadd45β polypeptide spanning from residue 69 to 104 participates in an interaction with JNKK2

[00079]	This amino acid region contains the domain of Gadd that is also responsible for the interaction with JNKK2
[00084]	"FIG. 30 shows that peptide 1 impairs the ability of Gadd45β (and NF-κB) to suppress JNK activation ...." Gadd blocks JNK signaling.
[00087]	"Potential means for achieving this interference include, for instance, using blockers of Gadd45β."
[00090]	"... design of agents to modulate the JNK pathway e.g., cell permeable, fusion peptides (such as TAT-fusion peptides) "small molecules" and other compounds.
[000189]	"natural and synthetic chemical compounds."
[00194-000210]	Sufficient demonstrations of agents that block the Gadd45β suppression are in the application to award the inventor a claim beyond one embodiment.
[000202]	Methods to assess modulators.
[00211-215]	Natural and synthetic chemical compounds.

III. Claims satisfy §112 enablement requirements

Claims 1, 2, 6, and 36 were rejected under 35 U.S.C. 112, first paragraph enablement requirement.

The examiner, while acknowledging that the specification disclosed a fusion peptide that "was capable of functioning as claimed", (page 4, Office Action mailed 11/29/06), stated further that the specification:

...fails to describe a representative number of species that function as claimed, or structural features common to members of genus, or a correlation between structure and function for members of the genus." (p. 4 of the Action).

The invention includes the discovery and testing of the Gadd45β interaction with JNKK2 of the JNK pathway, suppressing it.

The specification as filed provides a working example of a fusion peptide with a specific sequence structure. For example, the specification discloses that a peptide comprising a sequence of GPVWKMRFRKTGHVIAVKQMRRSGN functions a specific blocking peptide that blocks Gadd45β inactivation of JNK pathway. This sequence has a specific structure (the peptide sequence" and this structure is correlated with a specific function, i.e., blocking Gadd45β interaction with JNKK2. The law does not require that every conceivable embodiment to be tested and validated. The inventors of the present application discovered a novel mechanism of inhibition of JNK pathway by Gadd45β and this inventive concept is intended to be covered by the claims. The fusion peptide is just one such method of inhibiting Gadd45β and JNKK2 interaction.

In addition, on page 3 of the Action, the examiner dismissed Dr. Franzoso Declaration Data as not being persuasive because:

(i) the data does not show the treatment of any disease, as is contemplated by the specification and is encompassed by the broadly drawn claims, and

(ii) the data does not show the use of an agent that interacts with Gadd45β....but rather shows the physiological effects of complete Gadd45β gene knock-out.

None of the pending claims mention any particular disease in the preamble. In addition, complete gene knock-outs, as mentioned in Dr. Franzoso's declaration are a commonly practiced technique to understand protein-protein interactions, including inhibition. For example, gene knock-outs provide a basis for antisense or RNAi-mediated gene targeting, where an agent (e.g., antisense RNA or an interfering RNA) is involved. Although the examiner acknowledges that the PTO is not the FDA, the examiner uses the requirements of §112 as an option to impose FDA requirements for treating diseases. Therefore, the Action, without due consideration, does not give any deference to the Gadd45β knock-out data that validates the Gadd45β's involvement in programmed cell death and cell growth.

The effects claimed are blocking suppression of activation of JNK thereby leading to increased cell death. The *in vitro* models used are standard and have been shown to reasonably correlate to *in vivo* effects. Apoptosis is the active participation of the cell in its own destruction through the execution of an intrinsic suicide program. Some of the factors in apoptosis have been studies by those of skill in the art using knock-out models, such as that used in the inventors' declaration.

The specification also provides data showing that a cell permeable peptide having a peptide sequence derived from JNKK2-Gadd45β binding region binds to Gadd45β and thereby prevents the Gadd45β-dependent inhibition of JNKK2. Thus, the cell-permeable peptide, e.g., peptide GPVWKMRFRKTGHVIAVKQMRRSGN (designated as Peptide 1) relieves the JNKK2 suppression by Gadd45β. In other words, Gadd45β present in the cells binds to this peptide in a competitive fashion and not to JNKK2, thereby allowing JNKK2 to promote JNK activation and the ensuing cell death. This cell death, i.e., apoptotic cell death is beneficial to reduce the growth of cancer cells.

Showing that Gadd45ß binds to and inhibits JNKK2 *in vitro*, thereby removing a barrier to apoptosis, coupled with the evidence that absence of Gadd 45ß *in vivo* removes a barrier to apoptosis, is sufficient to support the pending claims.

Claims Need Not Be Limited to Embodiments:

Claims 1, 2, 6, and 36 are rejected Under 35 U.S.C. §112, 1st par.

It is well established that claims need not be limited to embodiments, as the examiner is requesting.

As the Federal Circuit stated eloquently:

> If everything in the specification were required to be read into the claims, or if structural claims were to be limited to devices operated precisely as a specification-described embodiment is operated, there would be no need for claims. Nor could an applicant, regardless of the prior art, claim more broadly than that embodiment. ... It is the claims that measure the invention. *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1326 (Fed. Cir. 2002).

To limit claims to the HIV-TAT-Peptide 1 fusion is unduly restrictive, giving no credence to the inventors' overall invention—modulation of JNKK2 by Gadd 45ß. Peptide 1 is an example to show that an agent can disrupt the Gadd45β-JNKK2 binding as measured by its effects. The claims should not be limited to that embodiment, because the inventors of the present application have demonstrated for the first time, that preventing Gadd45β-JNKK2 interaction or binding results in increased cell death.

> [00090] **cell permeable, fusion peptides** (such as TAT-fusion peptides) encompassing the amino acid regions of JNKK2 that come into direct contact with Gadd45β. These peptides will effectively compete with endogenous Gadd45β proteins for binding to JNKK2.

Claims need not be limited to the preferred embodiment when the invention is more broadly described. *Inpro II Licensing, S.A.R.L. v. T-Mobile USA, Inc.*, 450 F.3d 1350, 1355 (Fed. Cir. 2006). The Court has cautioned against limiting the claimed invention to preferred embodiments or specific examples in the specification. *Varco, L.P. v. Pason Sys. USA Corp.*, 436 F.3d 1368, 1375 (Fed. Cir. 2006).

IV. Claims 1 and 36 satisfy 35 U.S.C. §112 second paragraph

Amended claims satisfy §112 2nd paragraph requirements.

Applicant disagrees there is no support for the term "interacts" in claim 1. The specification provides support for "interact" at least at the following instances (paragraph numbers refer to the published version of the application) see also Section II herein:

> [0109] *In vitro* GST pull-down experiments have confirmed a strong and direct interaction between Gadd45β and JNKK2....
>
> [0114] FIG. 19 shows physical interaction between Gadd45β and kinases in the JNK pathway, *in vivo*. ....., the ability of Gadd45β to physically interact with additional kinases in the JNK pathway was examined, focusing on those MAPKKKs, MAPKKs, and MAPKs that had been previously reported to be induced by TNF-Rs. ..... Notably, Gadd45β also interacted with JNKK2/MKK7, but not with the other JNK kinase, ... The interaction with JNKK2 might also explain the specificity of the inhibitory effects of Gadd45β on the JNK pathway.
>
> [0115] FIG. 20 shows physical interaction between Gadd45.beta. and kinases in the JNK pathway, in vitro.....
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> [0116] FIG. 21 shows Gadd45β inhibits JNKK2 activity in vitro. Next, the functional consequences, in vitro, of the physical interactions of Gadd45β with kinases in the JNK pathway was assessed.....

> [0117] FIGS. 22A-B shows Gadd45β inhibits JNKK2 activity in vivo. The ability of Gadd45β to inhibit JNKK2 was confirmed in vivo, in 3DO cells.....
>
> [0120] FIGS. 23A-B shows that two distinct polypeptide regions in the kinase domain of JNKK2 are essential for the interaction with Gadd45β. By performing GST pull-down assays with GST- and GST-Gadd45β-coated beads, the regions of JNKK2 that are involved in the interaction with Gadd45.beta. were determined.....
>
> [0122] The finding that Gadd45β directly contacts two distinct amino acid regions within the catalytic domain of JNKK2 provides mechanistic insights into the basis for the inhibitory effects of Gadd45β on JNKK2....
>
> Example 12: JNKK2 (Also Known as MKK7)-Gadd45β Interacting Domains....

However, the term is replaced by amendments to relate suppression of JNK activation by Gadd45β.

V. Other Issues

Claim 37 is withdrawn, making the 112 rejection moot.

If pending claims are allowable, and a terminal disclaimer over U.S. Serial No. 10/263,330 is necessary, it will be filed.

Applicant requests the present amendment is entered for allowance or appeal. If there are still issues, an interview is also requested.

No other fees are believed due at this time, however, please charge any deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (21416-94575).

Respectfully submitted,

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